

**A COMPARISON OF HEALTH CARE UTILIZATION AND COSTS
ASSOCIATED WITH INHALED CORTICOSTEROID VERSUS
BETA₂-AGONIST THERAPY IN THE MANAGEMENT OF ASTHMA
AT DARNALL ARMY COMMUNITY HOSPITAL**

by

TRISH PHU BUI, B.S.

THESIS

**Presented to the Faculty of the Graduate School
of The University of Texas at Austin
in Partial Fulfillment
of the Requirements
for the Degree of**

MASTER OF SCIENCE IN PHARMACY

The University of Texas at Austin

August 2000

DISTRIBUTION STATEMENT A
Approved for Public Release
Distribution Unlimited

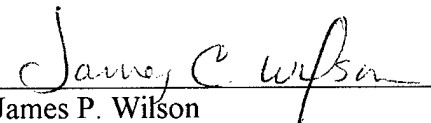
20001019 150

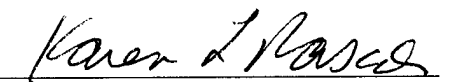
A COMPARISON OF HEALTH CARE UTILIZATION AND COSTS
ASSOCIATED WITH INHALED CORTICOSTEROID VERSUS
BETA₂-AGONIST THERAPY IN THE MANAGEMENT OF ASTHMA AT
DARNALL ARMY COMMUNITY HOSPITAL

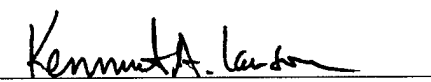
APPROVED BY

SUPERVISING COMMITTEE:

Supervisor:


James P. Wilson


Karen L. Rascati


Kenneth A. Lawson

DEDICATION

To my parents for all their love and support.

To my children, Hope, Peter, and Andrew, who are the center of my universe.

Most importantly, to my husband Steve for his love, patience, and devotion.

ACKNOWLEDGMENTS

I am grateful to Drs. James Wilson, Karen Rascati, and Ken Lawson for their guidance and support throughout my study. The faculty, staff, and fellow graduate students in the Pharmacy Administration Division of The University of Texas at Austin College of Pharmacy have also been very supportive. Finally, I would be profoundly remiss if I didn't thank Major Gwendolyn Thompson and Ms. Stephanie Laird at Darnall Army Community Hospital for their support in this study.

Trish P. Bui

The University of Texas at Austin

August 2000

ABSTRACT

A COMPARISON OF HEALTH CARE UTILIZATION AND COSTS ASSOCIATED WITH INHALED CORTICOSTEROID VERSUS BETA₂-AGONIST THERAPY IN THE MANAGEMENT OF ASTHMA AT DARNALL ARMY COMMUNITY HOSPITAL

by

Trish Phu Bui, M.S. Phr

The University of Texas at Austin, 2000

SUPERVISOR: James P. Wilson

Objective: Previous studies have found that the use of inhaled steroids to control asthma results in significant economic and clinical benefits when compared to alternative pharmacologic therapies. National and international guidelines on the management of asthma state that inhaled steroids are the preferred treatment in the management of persistent asthma. The aim of this study was to compare the economic impact of inhaled steroid versus beta₂-agonist use in the management of asthma at Darnall Army Community Hospital.

Methods: A retrospective, database study was undertaken in 195 persistent asthmatics, regardless of age, from October 1998 to March 1999. The

treatment groups being compared were those using inhaled beta₂-agonists versus inhaled corticosteroids. Patients with COPD were excluded from the study. Variables of interest were health care utilization and costs associated with prescriptions, physician visits, emergency department (ED) visits, and hospitalizations. This study took the perspective of the institution; therefore, only direct costs were considered.

Results: Patients in the inhaled steroid group had higher health care utilization and associated costs than those in the beta₂-agonist group. On the average, steroid users consumed 3.11 more prescriptions, 1.55 more physician visits, 13 more hospital admissions, and 0.2 more ED visits than beta₂-agonist users. Medical costs for steroid users were \$405.93 higher, drug costs were \$78.95 higher, and total health care costs were \$484.87 higher than for beta₂-agonist patients.

Conclusions: In contrast to findings from previous work, this study showed no evidence in economic benefits from the use of inhaled steroids when compared to beta₂-agonists in terms of cost savings associated with lower health care utilization. The results of this study may have been greatly influenced by the study design that led to unmatched treatment groups. Compared to the beta₂-agonist group, patients in the steroid group may have been sicker to begin with, and thus, incurred greater utilization and costs.

TABLE OF CONTENTS

LIST OF TABLES	ix
CHAPTER ONE – INTRODUCTION	1
SECTION I – BACKGROUND	3
PATHOGENESIS	3
PREVALENCE	4
COST OF ILLNESS	5
SECTION II – MANAGEMENT OF ASTHMA	7
NIH GUIDE TO PHARMACOTHERAPY	8
TREATMENT CATEGORIES	11
SECTION III – REVIEW OF INHALED STEROID STUDIES ...	18
EFFICACY STUDIES	18
ECONOMIC STUDIES	21
SECTION IV – PURPOSE	25
SECTION V – OBJECTIVES	26
SECTION VI – HYPOTHESES	27
CHAPTER TWO – METHODOLOGY	28
STUDY POPULATION	28
STUDY DESIGN	29
IRB APPROVAL	29
DATA SOURCE	30
DATA COLLECTION	31
DATA ANALYSIS	35
CHAPTER THREE – RESULTS	36
STUDY SAMPLE	36
DEMOGRAPHIC DIFFERENCES	37
DISTRIBUTION OF EXPENDITURES	38
DIFFERENCES IN UTILIZATION	39
DIFFERENCES IN HEALTH CARE COSTS	41

CHAPTER FOUR – DISCUSSION AND CONCLUSIONS	43
TREATMENT GROUPS	43
DISTRIBUTION OF EXPENDITURES	44
TESTS OF HYPOTHESES	45
SUBGROUP ANALYSIS (HIGH USERS)	49
ASSUMPTIONS AND LIMITATIONS	54
IMPLICATIONS FOR DACH	56
SUGGESTIONS FOR FUTURE RESEARCH	57
CONCLUSION	57
APPENDICES	
A. Fields Included within the Composite Health Care System (CHCS) Prescription File	59
B. Fields Included within the Inpatient Data File	60
C. Fields Included within the Ambulatory Data File	61
D. Unit Costs Used in Computing Medical Care Expenditures	62
E. Medications and Their Associated Costs Included in This Study	63
F. ICD-9-CM Codes Used to Verify Diagnosis of Asthma	64
G. Tests of Normality	65
H. Age Distribution of Study Sample	66
I. Gender Distribution of Study Sample	67
J. Prescription Usage of Study Sample	68
K. Age Distribution of High Users	69
L. Gender Distribution of High Users	70
M. Prescription Usage of High Users	71
REFERENCES	72
VITA	77

LIST OF TABLES

Table 1.1	Stepwise Approach to Long-Term Management of Asthma for Adults and Children over Age Five	10
Table 1.2	Stepwise Approach to Long-Term Management of Asthma for Children Five and Younger	11
Table 1.3	Anti-Asthma Drugs	12
Table 3.1	Gender and Age Distributions of Asthma Subjects Managed with Inhaled Beta ₂ -Agonist and Corticosteroid Therapy	37
Table 3.2	Asthma-Related Expenditures by Category for 195 Study Subjects from October 1998 to March 1999	39
Table 3.3	Asthma-Related Health Care Utilization by Treatment Group from October 1998 to March 1999	40
Table 3.4	Asthma-Related Health Care Costs by Treatment Group from October 1998 to March 1999	41
Table 4.1	Characteristics of High Users by Age Category	50
Table 4.2	Asthma-Related Health Care Utilization for High Users by Age Category from October 1998 to March 1999	51
Table 4.3	Asthma-Related Health Care Costs for High Users by Age Category from October 1998 to March 1999	53

CHAPTER ONE

INTRODUCTION

In the United States, over 20 million people are affected by asthma (Barbers 1998). Despite the advance in knowledge of the pathogenesis and effective treatment of asthma, morbidity and mortality continued to rise. The burden of this disease can be heavy on patients, their families, the health care system, and society (CDC 1995, Pal 1997, Smith *et al.* 1997). Because of this paradox, the National Institute of Health (NIH) has led a reevaluation and issued revised treatment guidelines for the diagnosis and management of this disease.

The economic burden of asthma was estimated to be \$11.3 billion in the United States for 1998 (NIH 1999). Emergency department visits and hospitalizations accounted for a large portion of that figure. Those events often can be prevented with patient education, appropriate therapy, and patient compliance (DeTullio *et al.* 1987, Lenfant 1995). In addition, a variety of disease management programs have been implemented with favorable clinical and economic outcomes (MacKinnon *et al.* 1996, Mayo *et al.* 1990, Sleath *et al.* 1997).

The primary goal of this study is to retrospectively determine the costs and health care utilization of two alternative therapies in the management of persistent asthma at Darnall Army Community Hospital. This study takes the

perspective of the institution; therefore, only direct medical expenditures will be evaluated.

Costs associated with health care utilization have been employed in at least one previous retrospective record-based study (Ross *et al.* 1988) to assess treatment effectiveness. The logic behind this hypothesis is that lower health care utilization and costs associated with a particular treatment are indicative of greater effectiveness. In the present study, health care utilization and costs associated with inhaled beta₂-agonist and corticosteroid therapies will be estimated and compared for differences in treatment benefits.

SECTION I

BACKGROUND

This section discusses the pathogenesis, prevalence, and cost of illness of asthma.

PATHOGENESIS

Asthma is a variable disease characterized by increased airway responsiveness to various stimuli. It is the most common chronic illness in childhood and is manifested by general airway obstruction that changes in severity (CDC 1996, Taylor *et al.* 1992). Clinical manifestations of asthma include episodic shortness of breath, wheezing, coughing, and chest tightness. Acute episodes can be fatal in rare instances. Ordinarily, the beginning symptoms are brief and periodic; however, with time they can become more frequent and severe (McFadden *et al.* 1992).

The following characteristics are used in the definition of asthma: (1) airway inflammation, (2) airway hyperresponsiveness, and (3) reversible airway obstruction (PEC 1996). In bronchial hyperresponsiveness, the airways constrict in response to a variety of nonspecific stimuli such as cold air, allergens, environmental pollutants, or even therapeutic drugs (McFadden *et al.*

1992). The degree of hyperresponsiveness is related to the severity of the disease, and any changes in reactivity may result in changes in airway inflammation. Significant airway inflammation has long been associated with severe and often fatal asthma; however, it has been documented that inflammation is present even in patients with mild asthma (Larsen 1992).

PREVALENCE

In the United States, over 20 million people are afflicted with asthma (Barbers 1998). It is a leading cause of morbidity in childhood (CDC 1996, Gergen *et al.* 1988, Taylor *et al.* 1992). With an estimated 2.2 million ambulatory care visits each year, asthma and wheezing are among the 10 most frequent reasons for visits to pediatricians in the U.S. (Weitzman *et al.* 1992). Over the past 20 years, the burden of asthma has been increasing, with children and blacks being affected more than other segments of the population (CDC 1996, NIH 1999, Pal 1997). Within the general population, the prevalence was higher among females than males; however, among children, the prevalence was higher among males (NIH 1999). In a national survey of asthma prevalence among children in the U.S. from 1976 to 1980, an overall 6.7% of youths was affected by asthma, with blacks more than whites, boys more than girls, and urban more than rural areas. The survey also reported a higher prevalence of other allergies and allergen skin test reactivity in asthmatic children than

nonasthmatic children. Furthermore, most asthma sufferers had their first attack before their third birthday (Gergen 1988).

According to an update issued by the Department of Defense (DoD) Pharmacoeconomic Center (PEC 1996), compared to the general population, the distribution of asthma within the DoD is skewed toward the pediatric group, because a history of asthma makes an individual unfit for military duty. Exceptions are made for members with mild, intermittent disease.

COST OF ILLNESS

Asthma is a common disease affecting 1 in 25 Americans and over 100 million people worldwide. It is a source of much physical impairment, leading to lost productivity and school days, and high economic burden to the health care system. In the 1980s, hospitalizations and deaths from asthma increased despite the emergence of more effective asthma therapies (CDC 1995, Lenfant 1995, Weiss *et al.* 1993). It appears that the main reason for the high burden asthma places on health care resources is the underdiagnosis and undertreatment of the disease (Mellis *et al.* 1993). In 1995, asthma caused over 1.5 million emergency department visits, 500,000 hospitalizations, and over 5,500 deaths. The estimated economic burden of this disease totaled \$11.3 billion in 1998, with direct costs accounting for \$7.5 billion and indirect costs of \$3.8 billion (NIH 1999). The Department of Defense spends more than \$19 million per year

on the drug treatment of asthma (PEC 1996). The DoD annual cost of beclomethasone oral inhalers alone between July 1997 and June 1998 was \$490,000 (PEC 1999). Despite the significant spending, many DoD patients are not receiving appropriate asthma treatment (PEC 1996).

Asthma exacerbations often result in loss of productivity, school absenteeism, and decreased quality of life. Reducing and preventing airway hyperresponsiveness and treating associated conditions, such as infections or allergies, are the essential treatment strategies for asthma (Slack *et al.* 1995). Cost of treatment to control asthma can be high, and when the disease is not adequately controlled, treating acute attacks can consume substantial health care resources (Smith *et al.* 1997, Weiss *et al.* 1992). Failure to follow national and international guidelines appeared to be associated with high consumption of health care resources (Stempel *et al.* 1996).

SECTION II

MANAGEMENT OF ASTHMA

One of the reasons for the increase in asthma morbidity and mortality is the underdiagnosis and undertreatment of the disease (Lenfant 1995, Mellis *et al.* 1993). Reasons for these deficiencies are numerous, ranging from not recognizing that a person has asthma to not treating episodes appropriately. One important element contributing to the undertreatment of asthma is not grasping the need to treat the underlying inflammation. Short-acting beta₂-agonists treat only bronchospasm and cannot reduce or prevent the inflammation. Daily antiinflammatory treatment should be prescribed for patients with chronic asthma (Barnes 1997, Lenfant 1995).

Although the course and clinical manifestations of asthma are similar worldwide, treatment differs considerably from country to country (Barnes 1997). Management of asthma often involves complex regimens and multiple medications, making a patient's adherence to prescribed treatment plan difficult. Also, adverse effects from medications often have a negative impact on treatment compliance (Slack *et al.* 1995). Currently, greater emphasis is placed on treating asthma as an inflammatory disease, and more and more attention is focused on the use of antiinflammatory agents to control asthma more

effectively, reduce morbidity and mortality, and improve patients' quality of life (Barnes 1997, Lenfant 1995).

In its second expert panel report (NIH 1997), the National Asthma Education and Prevention Program (NAEPP) has published updated guidelines for the diagnosis and management of asthma. The highlights of those recommendations are summarized as follows:

- Emphasis on asthma as an inflammatory disease
- Early and aggressive treatment with inhaled corticosteroids
- The need for categories of medications as controllers for maintenance and rescue therapy for quick relief
- Reclassification of asthma severity as mild intermittent, mild persistent, moderate persistent, or severe persistent
- Use of antileukotrienes for mild persistent asthma
- Monitoring of lung function tests to include spirometry initially and every 1 to 2 years and with peak flow meters at home
- Identifying and avoiding environmental stimuli
- Emphasis on education and corroboration with health care providers, patients, and their families

NIH GUIDE TO PHARMACOTHERAPY

Asthma management should be guided by the severity of the disease, benefits and risks of each treatment, and cost effectiveness of treatments. The severity of asthma is categorized based on airflow restriction and its variability.

The NAEPP Second Expert Panel's guidelines for the management of asthma include four major components: (1) measures of assessment and monitoring, (2) control of factors contributing to asthma severity, (3) pharmacologic therapy, and (4) patient education. These new guidelines reiterate that asthma is a disease of many factors and that pharmacologic management is only a portion of the overall strategy. In addition, nonpharmacologic intervention and prevention programs should also be developed and implemented. The goal of asthma management is to achieve control of asthma with the least amount of medication and minimal adverse effects (NIH 1997).

The Expert Panel further recommends a stepwise approach to asthma therapy for the management of chronic asthma. The type and frequency of medication are increased with increasing asthma severity. The aim is to achieve control with the least possible medication. Once control is reached at any step and maintained for about 3 months, a stepdown in therapy can be cautiously considered. The stepwise approaches to long-term asthma control for adults and for infants and young children are summarized in Tables 1.1 and 1.2, respectively (NIH 1997).

Table 1.1. Stepwise Approach to Long-Term Management of Asthma for Adults and Children Over Age Five.

Category	Long-Term Preventive (Preferred treatments are in bold print)
Step 4 Severe Persistent	<ul style="list-style-type: none"> • Inhaled corticosteroid, 800-2000mcg or more daily • Long-acting bronchodilator: either long-acting inhaled β_2-agonist, sustained-release theophylline, &/or long-acting β_2-agonist tablets or syrup, and • Corticosteroid tablets or syrup long-term.
Step 3 Moderate Persistent	<ul style="list-style-type: none"> • Inhaled corticosteroid, 800-2000mcg and • Long-acting bronchodilator, especially for nighttime symptoms: either long-acting inhaled β_2-agonist, sustained-release theophylline, or long-acting β_2-agonist tablets or syrup.
Step 2 Mild Persistent	<ul style="list-style-type: none"> • Either inhaled corticosteroid, 200-500mcg, cromoglycate, nedocromil, or sustained-release theophylline • May increase inhaled corticosteroids to 800mcg or add long-acting inhaled β_2-agonist, sustained-release theophylline, or long-acting β_2-agonist tablets or syrup.
Step 1 Intermittent	<ul style="list-style-type: none"> • None needed

As an adjunct to the recommendations for long-term therapy, bronchodilators, such as short-acting inhaled β_2 -agonists, can be used for quick relief at all stages.

Table 1.2. Stepwise Approach to Long-Term Management of Asthma for Children Five and Younger.

Category	Long-Term Preventive (Preferred treatments are in bold print)
Step 4 Severe Persistent	<ul style="list-style-type: none"> • Inhaled corticosteroid MDI with spacer and face mask >1mg daily or nebulized budesonide >1mg b.i.d. • If needed, add oral steroids lowest possible dose on an alternate-day, early morning schedule
Step 3 Moderate Persistent	<ul style="list-style-type: none"> • Inhaled corticosteroid MDI with spacer and face mask 400-800 mcg daily or • Nebulized budesonide 1mg b.i.d.
Step 2 Mild Persistent	<ul style="list-style-type: none"> • Either inhaled corticosteroid, 200-400mcg or cromoglycate (MDI with a spacer and face mask or use a nebulizer)
Step 1 Intermittent	<ul style="list-style-type: none"> • None needed.

TREATMENT CATEGORIES

There are two broad categories of asthma medications: those used to prevent and/or decrease the frequency of symptoms (“controller”), and those taken to relieve asthma symptoms (“reliever”). The preferred type of preventive medication includes inhaled antiinflammatory agents such as corticosteroids, cromolyn, and nedocromil. They should be taken on a regular basis even in the absence of symptoms. Other long-term medications may include theophylline, slow-release oral and long-acting inhaled beta₂-agonists such as formoterol or salmeterol. Medications to relieve symptoms are prescribed to be taken only as

needed (p.r.n.). This category includes short-acting β_2 -agonists such as albuterol or terbutaline. They act quickly to relieve broncho-constriction and the accompanying symptoms such as cough, wheezing, and chest tightness. They are also labeled as rescue medication (NIH 1997). For patients who are not fully responsive to inhaled bronchodilators, a short course of oral corticosteroids may be used to treat acute exacerbations (Lenfant 1995). Any asthma more serious than mild intermittent asthma is more effectively controlled by treatment to prevent and reverse the inflammation than by treatment of only acute bronchoconstriction and accompanying symptoms (PEC 1996). The following table summarizes the different categories of asthma medications.

Table 1.3. Anti-Asthma Drugs.

Controllers	Relievers
Inhaled corticosteroids	Short-acting inhaled β_2 -agonists
Systemic corticosteroids	Systemic corticosteroids
Cromolyn	Inhaled anticholinergics
Nedocromil sodium	Short-acting theophylline
Sustained-release theophylline	Short-acting oral β_2 -agonists
Long-acting inhaled & oral β_2 -agonists	

ANTIINFLAMMATORY DRUGS

The pathogenesis of asthma is centered around chronic inflammation; therefore, the use of agents that stifle this process, such as corticosteroids, is critical. These drugs must be administered regularly on a long-term basis because they do not have a rapid effect and do not provide immediate symptom relief. Early use of these drugs in the disease process may provide longer lasting asthma control (Barnes *et al.* 1993, PEC 1996). There is also evidence to suggest that the single most important step in decreasing morbidity from acute attacks is the early use of corticosteroids and decreased excessive dependence on bronchodilators (Mellis *et al.* 1993).

Inhaled corticosteroids are the most potent antiinflammatory agents available for the treatment of asthma, and also the drugs of choice in reversing airway inflammation (Barnes *et al.* 1993, Mellis *et al.* 1993, Portyansky 1999). Yet practitioners often do not follow the NIH recommendation regarding the use of these drugs (Self *et al.* 1997), partly because of fears of adverse effects (Barnes 1989). Long-term corticosteroid treatment has been linked to systemic side effects such as growth suppression (Doull *et al.* 1995, Verberne *et al.* 1997), hypothalamic-pituitary-adrenal axis suppression (Holt *et al.* 1990), bone density reduction (Hanania *et al.* 1995, Wong *et al.* 2000), and cataracts (Cumming *et al.* 1997). These systemic effects, especially growth suppression in children, remain a concern for physicians and a source of reluctance in steroid

use. However, lower dosages (below 400 mcg/day) have been shown to be safe in adults and children (Barnes *et al.* 1993, Larsen 1992, Mellis *et al.* 1993). An inhaled corticosteroid is the appropriate first-line treatment for patients who need beta₂-agonists inhalation therapy more than once daily (Barnes *et al.* 1993, PEC 1996). Treatment of early, mild asthma with an inhaled steroid was found to be “effective and worthwhile” in a Helsinki study (Metso *et al.* 2000) comparing the efficacy of an inhaled steroid (budesonide) with that of a beta₂-agonist (terbutaline) in a group of adult patients.

Currently in the U.S., the available inhaled corticosteroids include beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, and triamcinolone acetonide. At low doses, they are considered to be effective and safe to use in children. Side effects from inhaled steroids are uncommon with low doses (< 400 mcg daily) and are mostly associated with the oropharyngeal deposit of the inhaled particles. The most common side effects include oropharyngeal candidiasis, hoarseness, sore throat, and coughing. These side effects may be prevented by rinsing the mouth or by using large volume spacers (Barnes 1997).

Two other antiinflammatory agents deserve mentioning. Cromolyn and nedocromil can be used as alternative therapy to low-dose inhaled corticosteroids in mild persistent asthma. These agents have good safety profiles and can be used on an as-needed basis to prevent symptoms resulting

from anticipated exposure such as cold air, exercise, and allergens. Nedocromil may also be used in conjunction with inhaled steroids in moderate asthma (Portyanski 1999).

A newer group of antiinflammatory agents have emerged which hold the advantage of oral dosing. Leukotriene receptor antagonists may also be used as alternative therapy to inhaled corticosteroids in mild persistent asthma. Their role in asthma control has not been thoroughly substantiated (Portyanski 1999).

BRONCHODILATOR DRUGS

Bronchodilators alone may not affect airway inflammation and may mask the underlying inflammation by briefly relieving symptoms. Inhaled beta₂-agonists are potent and effective bronchodilators. These drugs relieve reversible bronchospasm by relaxing the bronchiole smooth muscles. Most of these drugs act within minutes and are effective for 3 to 6 hours. They should be used as needed for the relief of symptoms. There is evidence to suggest that regular or increased use of beta₂-agonists worsens asthma or indicates deteriorating control (Aldridge *et al.* 2000, Mellis *et al.* 1993). Patients on high doses of inhaled bronchodilators are associated with asthma-related treatment charges that were three times higher than for the average asthmatic patient. Inpatient and emergency department charges also increased in high bronchodilator users (Stempel *et al.* 1996).

Some of the common short-acting beta₂-agonists available in the U.S. include albuterol, metaproterenol, and terbutaline. The oral beta₂-agonists are not indicated for children except those who are unable to use the inhaled preparations. Recently introduced are the long-acting beta₂-agonists, formoterol and salmeterol. They are approved for use in patients with moderate or severe persistent asthma who require regular beta₂-agonist therapy. They are also effective for patients with nocturnal symptoms and for the prevention of exercise-induced bronchospasm. These drugs are not indicated for patients who can be managed with as-needed inhaled beta₂-agonists. They have a longer onset of action and thus, should not be used for management of acute attacks (Portyanski 1999). Long-acting beta₂-agonists may provide better control than increasing the dose of inhaled steroids when asthma is not sufficiently controlled in patients by low-dose steroids (Barnes 1997). If regular bronchodilator treatment is needed for asthma control, long-acting agents should be the preferred choice over short-acting ones (Sears 2000). Although inhaled long-acting beta₂-agonists are classified as long-term control medication, they have no antiinflammatory effects and do not replace antiinflammatory agents. They may be used in addition to inhaled steroids (Portyanski 1999).

Adverse effects of beta₂-agonists are usually not a problem for patients using recommended doses. High doses may cause muscle tremor, tachycardia, palpitations, and restlessness. The use of more than one canister per month is associated with increased risks of morbidity and mortality from asthma. In addition, high doses of inhaled beta₂-agonists may impede the antiinflammatory effects of steroids. Finally, tolerance to the antiasthmatic effects of inhaled beta₂-agonists may develop with long-term or high-dose use (Barnes 1997, Taylor *et al.* 1996).

SECTION III

REVIEW OF INHALED STEROID STUDIES

To date, numerous efficacy studies of inhaled steroid use have been published, but only a few involve economic evaluations. This section highlights some the clinical and economic studies of corticosteroid use in the treatment of asthma.

EFFICACY STUDIES

In a study to measure the effect of long-term budesonide treatment on asthma control in non-steroid-dependent asthmatics, Juniper and colleagues (1990) conducted a double-blind, randomized, controlled trial with 32 subjects requiring bronchodilators alone. The authors evaluated airway hyperresponsiveness, time course and characteristics of improvements, and associated changes in clinical asthma severity. Clinical asthma severity was assessed with a questionnaire, daily bronchodilator use, and number of exacerbations. Methacholine was administered to trigger and, hence, measure hyperresponsiveness. Although the placebo group remained very stable, the budesonide group showed a mean fourfold improvement in airway responsiveness ($p < 0.0005$). The authors also observed significant improvements

in asthma symptoms, bronchodilator use, and number of exacerbations. Their results show that regular, long-term use of inhaled steroid can confer significant improvements in airway responsiveness, sometimes with complete resolution.

Haahtela and colleagues (1991) conducted a comparison study of the effect of an inhaled steroid, budesonide, with that of an inhaled beta₂-agonist, terbutaline, in the long-term treatment of newly detected asthma. One hundred three patients aged 15 to 64 years were randomly assigned to one of two treatments for two years. Data from patients' diaries showed budesonide to be more effective than terbutaline in improving peak expiratory flow ($p<0.01$), reducing the symptoms of asthma ($p<0.01$), and reducing the use of supplemental beta₂-agonist ($p<0.01$). Ten patients dropped out of the terbutaline group due to inadequate effectiveness, whereas only one dropped out of the budesonide group. In a third-year follow-up study, the authors investigated whether the steroid dose could be decreased or discontinued, and what effect crossover of patients from beta₂-agonist therapy to steroid therapy would have. A dose reduction was effective in 74% of the patients, but discontinuation of treatment often resulted in exacerbations. Patients who were crossed over from terbutaline showed an improvement, although the degree was less than in those who were treated with budesonide at the study initiation. The authors concluded that early treatment with inhaled budesonide results in long-term control of mild asthma (Haahtela *et al.* 1994).

Donahue and colleagues (1997) conducted a retrospective cohort study to determine if antiinflammatory treatment would reduce the risk of asthma hospitalization in a health maintenance organization (HMO) setting. They found an inverse relationship between inhaled steroid use and hospitalization. Similar results were seen with the antiinflammatory agent cromolyn. In contrast, an association between increased use of beta-agonist and increased hospitalization was observed. The steroid-related protection was most noticeable among those who were high users of beta-agonist. Their results support the use of inhaled steroids to control asthma symptoms in those who require more than the occasional use of a beta-agonist.

In a placebo-controlled study published in 1998, Katz *et al.* (1998) compared fluticasone 50 mcg BID and fluticasone 100 mcg BID against placebo to demonstrate the efficacy and safety of low-dose steroid use in children with persistent asthma. The authors found significant improvements in peak expiratory flow (PEF) scores in both treatment groups as compared to placebo. No statistical difference was seen between the two treatment groups. Drug-related adverse events (asthma, dysphonia, cough, and oral candidiasis) were similar in all three groups.

Another study dealing with low-dose corticosteroid was conducted by Foresi *et al.* (2000). In this study, Foresi and colleagues compared budesonide 100 mcg BID (low dose) with that of 400 mcg BID (standard dose) in

controlling symptoms and lung function in subjects with moderate asthma. The authors also investigated whether or not a short-term increase in the daily dose of budesonide could treat acute exacerbations. The results of the study showed that low-dose budesonide is as effective as the standard dose in the control of symptoms and lung function. The authors also found that the dose increase at onset of asthma attack has an advantageous clinical effect.

ECONOMIC STUDIES

One of the earliest economic studies published was conducted at the Department of Pulmonary Medicine in Umea, Sweden. Alderoth and Thompson (1988) investigated the effects of replacing oral steroids with high-dose inhaled budesonide in 36 patients with severe steroid-dependent asthma. Comparing the two-year study period to the two years prior to the switch from oral steroids, the researchers found a 75% decrease in inpatient days. Inpatient admissions were reduced by half. A shift was seen from unscheduled to regular visits, but with an increase of 14%. An economic benefit resulting from the switch was a 55% decrease in the average annual costs of medical care for the Department of Pulmonary Medicine.

In a study to assess the efficacy and cost-effectiveness of inhaled steroids (beclomethasone and budesonide) in a developing country, 86 children with moderate to severe asthma, acting as their own controls, were followed for four

years to assess the impact of inhaled steroids as prophylaxis for asthma. Clinical efficacy endpoints were improvement in school attendance, hospitalizations, breakthrough wheezing, and acute severe attacks. Cost-effectiveness was estimated using expenditures for the family, on a cost of illness framework, before and after treatment. Significant improvements in all variables were seen after treatment ($p < 0.001$). Mean monthly cost and mean cost per unit satisfaction (cost utility value) decreased after starting treatment. Improvement in clinical parameters and reduction in mean costs led the investigator to conclude that, "even for developing countries with financial constraints, inhaled steroid treatment for prophylaxis of asthma is a cost effective and rational form of treatment." (Perera 1995)

Rutten-van Molken and colleagues (1995) conducted a 2.5-year randomized controlled study to determine the costs and effects of combined bronchodilator and antiinflammatory therapy on asthma and COPD. Two hundred seventy-four patients aged 16 to 60 years with moderately severe obstructive airways disease were randomly assigned to one of three treatment groups: combined beta₂-agonist/steroid, combined beta₂-agonist/anticholinergic, or beta₂-agonist/placebo. Clinical endpoints were lung function, hyperresponsiveness, restricted activity days, and symptom-free days. Economic endpoints were costs of health care utilization. The steroid group experienced significant improvements in clinical measures, whereas the

anticholinergic group did not differ from placebo. The annual acquisition cost for the steroid group was \$376 more than the placebo group. However, compared to the placebo group, the steroid group incurred \$454 less in other health care costs. Total health care costs (including treatment costs) for the steroid, anticholinergic, and placebo groups were \$652.50, \$722.90, and \$729.70, respectively. The authors reported that the slight increase in health care costs seen in the steroid group was compensated for by the benefits in clinical functions. In contrast, the addition of an anticholinergic agent appeared expensive and ineffective.

Balkrishnan and colleagues (1998), using the North Carolina Medicaid database, conducted a retrospective, cohort study to measure outcomes and cost benefits associated with inhaled steroid therapy. A comparison group of 180 patients was followed for one year before and one year after the start of inhaled steroid therapy. A control group of 233 patients of similar severity, who remained on any therapy other than steroids, were followed for two years. After the start of steroid therapy, hospitalizations for the comparison group decreased by 50%, outpatient visits (including emergency room visits) by 26%, and physician visits by 15%. The control group, in contrast, had significant increases in hospitalizations by 23% and outpatient visits by 36% at the end of the two-year period. All of the changes were statistically significant. Total

health care costs per patient per month decreased by almost 24% as a result of the initiation of inhaled steroid therapy.

In summary, these studies reported favorable results with inhaled corticosteroid use for the treatment of asthma. With regards to clinical functions, inhaled steroids were found to confer significant improvements and effectiveness in airway responsiveness and long-term control of asthma symptoms. Low-dose inhaled steroid use has been shown to be safe and effective in children. Significant cost savings and benefits have also been demonstrated with inhaled steroid use.

SECTION IV

PURPOSE

The question of interest for this study is as follows: Is the concurrent use of inhaled corticosteroid agents beneficial (in terms of lower health care utilization and associated costs) compared to beta₂-agonist monotherapy in the treatment of persistent asthma? The primary goal of this study is to estimate the health care utilization and costs associated with two prescribed regimens in the management of persistent or chronic asthma. Asthma-related health care utilization and associated costs of two therapeutic alternatives in the treatment of asthma will be compared to evaluate differences in treatment benefits. This study takes the perspective of the institution; therefore, the purpose is to evaluate the economic estimates of the direct medical expenditures specific to that institution.

The results of this study, along with recommendations, if appropriate, will be presented to the participating institution. This information may be useful in making formulary decisions and establishing treatment guidelines.

SECTION V

OBJECTIVES

The goal of this study is to provide a pharmacoeconomic analysis that may be used to estimate cost savings associated with interventions intended to reduce morbidity and mortality of asthma. Utilization and cost data for persistent asthmatics at Darnall Army Community Hospital, during the period of October 1998 to March 1999, will be analyzed. The two treatment groups to be compared are patients receiving inhaled corticosteroids and those receiving beta₂-agonists. Specifically, the objectives of this study are to:

1. Quantify and compare the prescription usage and drug acquisition costs associated with the two treatment groups.
2. Quantify and compare the utilization and costs of asthma-related physician visits associated with the two treatment groups.
3. Quantify and compare the utilization and costs of asthma-related hospitalizations associated with the two treatment groups.
4. Quantify and compare the utilization and costs of emergency department visits associated with the two treatment groups.
5. Estimate and compare the total cost of health care utilization (for objectives 1-4) associated with the two treatment groups.

SECTION VI

HYPOTHESES

For the purpose of this study, the hypotheses are stated in the null form.

- Ho₁: There is no difference in the prescription use and drug acquisition costs between the two treatment groups.
- Ho₂: There is no difference in the utilization and costs for asthma-related physician visits between the two treatment groups.
- Ho₃: There is no difference in the utilization and costs for asthma-related hospitalizations between the two treatment groups
- Ho₄: There is no difference in the utilization and costs for asthma-related emergency department visits between the two treatment groups.
- Ho₅: There is no difference in the total cost of asthma-related health care utilization; as measured by prescription use, outpatient visits, emergency department visits, and hospitalizations; between the two treatment groups.

CHAPTER TWO

METHODOLOGY

This chapter discusses the study population, study design, data source, data collection procedure, and data analysis employed in this study.

STUDY POPULATION

This study included all asthmatic patients (as documented by ICD-9-CM codes), regardless of age, who were eligible for medical care at Darnall Army Community Hospital (DACH) from 1 October 1998 through 31 March 1999, and who had apparent persistent asthma as ascertained by routine or continuous asthma-specific prescriptions and health care utilization.

Darnall Army Community Hospital, located in Fort Hood, Texas is the largest and busiest community hospital in the U.S. Army. The hospital, along with its satellite clinics, provides health care to over 180,000 soldiers, retirees, and family members. The active duty population of Fort Hood is estimated to be over 41,000. This figure comes out to be about 23% of the total beneficiary population. The gender distribution for the active duty population is approximately 79% males and 21% females (Horowitz *et al.* 2000).

STUDY DESIGN

Drug utilization evaluation is a practical tool to identify individual differences in drug use and to implement interventions that will improve patient outcomes. This study incorporates medical use information with pharmacy data for the analysis of health care utilization.

This study is of a retrospective, observational nature to assess health care utilization and costs associated with different types of pharmacologic management of asthma, specifically inhaled beta₂-agonist and inhaled corticosteroid. The research question was whether inhaled corticosteroids, as antiinflammatory agents, would reduce total health care utilization (as measured by prescription use, outpatient visits, emergency department visits, and hospitalizations) and associated costs when compared to beta₂-agonist use.

IRB APPROVAL

Formal permission was obtained from Darnall Army Community Hospital (DACH) to conduct this study using its patient population. Because DACH did not have an institutional review board of its own, the study protocol was submitted to the Clinical Investigation Committee at Brooke Army Medical Center (BAMC) at Fort Sam Houston, Texas. The Committee at BAMC granted its approval to proceed with the study in December 1999. Finally, the complete study proposal package was submitted to the Departmental Review Committee

of the Graduate School at The University of Texas at Austin, who granted formal approval to proceed with the study with an exemption from the Institutional Review Board (IRB) review.

DATA SOURCE

Prescription, utilization, and cost data were all obtained from the DACH computer system. Ad hoc reports were generated to obtain prescription and health care utilization data. The prescription data set was generated by the pharmacy department using the Composite Health Care System (CHCS). A special ad hoc report writer, named TRENDSTAR, was used by the Resource Management Office to generate utilization data. TRENDSTAR is an ad hoc report writer that contains information from the summary ambulatory data record (SADR) and the summary inpatient data record (SIDR).

Three separate data sets were generated for the period of 1 October 1998 through 31 March 1999. The first set extracted from CHCS contained prescription information including unique patient identifiers, patient name, age, gender, prescription date, drug name and quantity, prescriber name, and refill information. A complete list of the fields included in this data set is found in Appendix A. The inpatient data set contained information including patient unique identifiers, discharge date, ICD-9 code, diagnosis, and length of stay. The ambulatory data set contained information such as patient unique

identifiers, date of visit, clinic visited, ICD-9 code, and diagnosis. Appendices B and C contain complete lists of fields for the inpatient and ambulatory data sets, respectively. Pertinent information from all three data sets were then extracted and aggregated for the analysis. Cost data for drug acquisition were obtained from pharmacy records. Cost data for ambulatory and inpatient visits were collected separately from the DACH Resource Management Office. Appendix D contains a breakdown of unit costs used in computing medical care expenditures for this study.

DATA COLLECTION

Prescription Data

The prescription data set was obtained by ad hoc report for confirmed asthma patients (by ICD-9-CM codes) receiving at least one inhaled beta₂-agonist, corticosteroid, cromolyn, or nedocromil. This data set contained 3,070 patients with 7,700 prescription fills from October 1998 to March 1999. In an attempt to minimize the confounding effects of concurrent drug therapy (from antiinflammatory agents other than inhaled steroids), patients receiving cromolyn or nedocromil (as monotherapy or concurrently with regular therapy) were deleted from this data set. The cromones (cromolyn and nedocromil) are sometimes used in place of corticosteroids for the treatment of asthma (Barnes 1997). Their use has been shown to be cost-effective (Ross *et al.* 1988).

Therefore, beta₂-agonist users receiving cromones may report similar treatment benefits as steroid users. Since the focus of this study is with the inhaled steroid as the antiinflammatory treatment, the inclusion of the cromones may confound the study results. The addition of the cromones in the initial data set was to identify patients for subsequent removal. Forty-two patients belonged to this subgroup and were deleted, resulting in 3,028 patients remaining. The medications included in this study (and their unit costs) are listed in Appendix E.

Because persistent asthma is the target of this study, patients who had less than four months' supply of the study medications were deleted from the study. This deletion yielded 374 patients. To minimize any confounding effects from patients with comorbid chronic obstructive pulmonary disease (COPD), 44 patients with COPD (based on ICD-9-CM code 493.20) were deleted. Next, to ensure that all patients in the database received health care exclusively at DACH, those who received prescriptions from prescribers outside the institution were deleted (134 patients). In other words, these patients received prescriptions from providers outside of DACH and brought them in to the DACH Pharmacy to fill. One hundred ninety-six patients remained in this filtered data set (59 beta₂-agonist users with 252 prescription fills and 137 steroid users with 1,113 prescription fills).

Within this filtered data set, two categories of patients were constructed. One group composed of patients on beta₂-agonist monotherapy, and the second

group included patients on steroid therapy (alone or in combination with beta₂-agonist therapy). The proportion of steroid patients on combination therapy was 96.3%. All patients were allowed to be on other as-needed medications.

Intervention Group Identification

The prescription data set for the period of 1 October 1998 through 31 March 1999 was examined to identify patients with apparent persistent asthma. The intervention group consisted of patients whose asthma was managed by inhaled corticosteroids (alone or in combination with beta₂-agonist therapy). For the purpose of this study, persistent asthma is defined as a minimum of four 30-day-equivalent prescriptions for the treatment medications. The number of 30-day-equivalent prescriptions was determined from a combination of the quantity dispensed, the direction for use, and the unit size of the inhaler canister. From the directions for use, the number of puffs per month was computed. Then the number of canisters required can be estimated from the number of puffs computed. Taking the quantity dispensed and divide it by the number of canisters would yield the number of 30-day equivalent prescriptions.

Comparison Group Identification

The identification of the comparison group was accomplished in the same fashion as the intervention group. This group consisted of patients whose

asthma was managed with inhaled beta₂-agonist therapy. As with the intervention group, a minimum of four 30-day-equivalent prescriptions for inhaled beta₂-agonist therapy was a requirement for inclusion in this group.

Study Selection Criteria

Patient-unique identifiers were used to extract and aggregate data. ICD-9-CM codes (*International Classification of Diseases, 9th Revision, Clinical Modification* 1999) were used to capture asthma-specific ambulatory visits and hospital admissions. Because the prescription data file did not include the ICD-9-CM codes, patients from this database were cross-referenced with those in the ICD-9-CM code file to confirm diagnosis for asthma. The ICD-9-CM codes used in this study are listed in Appendix F.

Utilization and Cost Variables

The utilization variables used in this study included the actual number of prescriptions dispensed, the number of physician visits, the number of emergency department visits, and the number of hospitalizations. The cost variables included the institutional expenditures, in 1999 U.S. dollars, for drug therapy, physician visits, emergency department visits, and inpatient days.

DATA ANALYSIS

Due to the nature of this study, randomization was not possible. Matching was also not possible because of the lack of information regarding disease severity. As a result, an unbalanced design, with respect to unequal cell sizes, was arrived at for the analysis.

Distribution of Data

All analyses were conducted using SPSS 9.0 for Windows software. With visual inspection, the data were audited for outliers. Histograms, Q-Q plots, and tests for normality were conducted to ascertain the distribution of data (Norusis 1998). The results from the Kolmogorov-Smirnov tests of normality are found in Appendix G.

Tests of Hypotheses

Using independent groups statistical tests, the two treatment groups were tested for differences in inpatient, physician, and emergency department visits, and for differences in mean prescription usage. In addition, the costs for the individual variables, as well as the overall total for the two groups, were calculated and compared for differences. An alpha level of 0.05 was used to test for significance.

CHAPTER THREE

RESULTS

This chapter reviews the study sample, the demographic description of the treatment groups, and the results for the study objectives.

STUDY SAMPLE

For the period of 1 October 1998 through 31 March 1999, the prescription database at Darnall Army Community Hospital (DACH) contained over 3,028 asthma patients with 6,777 prescription fills for at least one of the study medications listed in Appendix D.

Using the study selection criteria described in the previous chapter, patients with COPD (N=44) and those with fewer than four prescriptions (N=2,654) of either bronchodilators or steroids were deleted, leaving 330 patients. Further deletion of prescriptions from outside providers (N=134) yielded 196 patients with 1,365 prescription fills. One patient was considered an outlier and was dropped from the study. This patient reported an inpatient cost of over \$17,900 in only one month.

For the final analysis, data for a total sample size of 195 patients were examined ($N_{\text{steroid}} = 136$, $N_{\text{beta-agonist}} = 59$). Examination of histograms, Q-Q plots, and Kolmogorov-Smirnov tests of normality for all continuous variables

showed that the assumption of normality for the study sample cannot be met (Appendix G). Furthermore, due to the unbalanced design, nonparametric tests were performed to test for statistical differences between the two treatment groups.

DEMOGRAPHIC DIFFERENCES

The distribution of steroid and beta₂-agonist patients with respect to gender and age is summarized in Table 3.1. As reported for the general population, the study population also contained more females than males. Of the 195 study subjects, 88 (45.1%) were males and 107 (54.9%) were females. Race/ethnicity was not available from the database for analysis.

Table 3.1. Gender and Age Distributions of Asthma Subjects Managed with Inhaled Beta₂-Agonist and Corticosteroid Therapy.

Variable	β ₂ -Agonist	Steroid	Total
Patients, No.	59	136	195
Gender, No.			
Male	28 (47.5%)	60 (44.1%)	88 (45.1%)
Female	31 (52.5%)	76 (55.9%)	107 (54.9%)
*Age, Yr.	37.3 (21.1) [37.0]	33.9 (21.1) [30.0]	34.2 (21.1) [35.0]
Age Range, Yr.	5 - 78	2 - 80	2 - 80

* Expressed as mean (standard deviation), [median]

As summarized in Table 3.1, gender distributions in both treatment groups were similar to the overall sample. Chi Square statistics showed that the gender distributions were not different between the two treatment groups ($\chi^2 = 0.185$, $df = 1$, $p = 0.667$).

With respect to age, the overall sample mean was 34.2 years (S.D. ± 21.1 years) and the median was 35.0 years. The mean and median ages for both groups were also similar. Within the beta₂-agonist group, the age range spanned from 5 to 78 years. The age range for the steroid group was 2 to 80 years. The Mann-Whitney U test showed that the age values for both groups were not statistically different ($Z = -1.463$, $p = 0.143$). Age and gender distributions for the study sample are further depicted in Appendices H and I.

DISTRIBUTION OF EXPENDITURES

The cost for each of the variables expressed in the study objectives was computed using the 1999 cost data for the institution. Table 3.2 summarizes the asthma-related health care expenditures for Darnall Army Community Hospital (DACH) for the 195 study subjects from October 1998 to March 1999.

Table 3.2. Asthma-Related Expenditures by Category for 195 Study Subjects from October 1998 to March 1999.

Category	Expenditure	Cost/member/month
Prescription	\$19,204 (19.8%)	\$16.41
Physician Office	39,815 (41.1%)	34.03
Inpatient	27,318 (28.2%)	23.35
Emergency Department	10,432 (10.8%)	8.92
Total	\$96,769 (99.9%)*	\$82.71

*Percentages do not add up to 100% due to rounding.

A total of \$96,769 was estimated for asthma-related medical and prescription expenditures for the study sample in this 6-month study period. Physician office visits accounted for the highest portion of this cost (41.1%), followed by hospitalizations (28.2%), drug acquisition (19.8%), and emergency department visits (10.8%). These individual costs were further broken down into cost per member per month.

DIFFERENCES IN UTILIZATION

Table 3.3 summarizes the results for the analysis of health care utilization. Compared to the beta₂-agonist group (N = 59), patients in the steroid group (N = 136) reported higher utilization in all four categories. Results from the Mann-Whitney U tests showed that prescription usage for the steroid group was statistically higher (Z=-6.969, p<.001) than for the beta₂-agonist group. Appendix J further illustrates prescription usage by the study sample. Physician office visits for the steroid group were also statistically higher (Z=-6.080,

$p < .001$). Of the 136 steroid users, 13 reported asthma-related hospital admissions. The mean length of stay for those 13 patients was 2.1 days (range: 1-6 days). The β_2 -agonist group reported no hospital admissions. The steroid group used 0.39 more emergency department visits than the β_2 -agonist group. Results from the Mann-Whitney U tests showed that the values for all variables were statistically different at the 0.05 level, except for emergency department visits.

Table 3.3. Asthma-Related Health Care Utilization by Treatment Group from October 1998 to March 1999.

Utilization Category	β_2 -Agonist Mean (S.D.) [Median] N = 59	Steroid Mean (S.D.) [Median] N = 136	Mann Whitney U Z Statistic (p)
Prescription, No.	5.03 (1.02) [5.00]	8.14 (3.35) [8.00]	-6.969 ($< .001$)
Physician office visits	0.75 (0.90) [0.00]	2.30 (1.89) [2.00]	-6.080 ($< .001$)
Inpatient days	0.00 (0.00) [0.00]	0.26 (0.94) [0.00]	-2.450 (0.014)
Emergency dept. visits	0.19 (0.51) [0.00]	0.39 (0.89) [0.00]	-1.590 (0.112)

DIFFERENCES IN HEALTH CARE COSTS

Total health care costs for both treatment groups during the six-month study period, along with individual components, are summarized in Table 3.4

Table 3.4. Asthma-Related Health Care Costs by Treatment Group from October 1998 to March 1999.

Cost Category	β_2 -Agonist Mean (S.D.) [Median] N = 59	Steroid Mean (S.D.) [Median] N = 136	Mann Whitney U Z Statistic (p)
Medical cost	\$114.66 (146.67) [63.00]	\$520.59 (851.69) [289.00]	-5.923 ($<.001$)
Inpatient	00.00 (00.00) [00.00]	200.87 (759.57) [00.00]	-2.450 (.014)
Outpatient	84.27 (104.47) [00.00]	256.20 (231.56) [170.50]	-5.883 ($<.001$)
Emergency	30.39 (82.75) [00.00]	63.52 (144.67) [00.00]	-1.590 (.112)
Drug cost	43.42 (46.76) [19.32]	122.37 (78.94) [96.45]	-7.896 ($<.001$)
TOTAL COST	\$158.09 (142.10) [145.32]	\$642.96 (855.10) [373.85]	-7.671 ($<.001$)

As seen in utilization patterns, the values for inpatient, outpatient, and drug costs were statistically different between the two groups. Mann-Whitney U tests showed that emergency department visits between the two groups were not statistically different ($Z=-1.590$, $p=0.112$). Overall, the Mann-Whitney U tests

showed that total health care costs were statistically different between the two treatment groups ($Z=-7.671$, $p<.001$). The steroid group incurred \$78.98 more in drug acquisition costs than the beta₂-agonist group. Medical cost was \$405.93 higher in the steroid group. Overall, the steroid group had a mean total cost (medical plus prescription usage) of \$484.88 higher than the beta₂-agonist group.

CHAPTER FOUR

DISCUSSION AND CONCLUSIONS

This chapter reviews the results for the objectives of this study. Assumptions, limitations, implications, and suggestions for future research are also discussed.

TREATMENT GROUPS

Drug acquisition and medical utilization costs were analyzed for 195 asthmatic patients for the first two quarters of fiscal year 1999. Of those 195 patients, 59 (30.9%) were identified as inhaled beta₂-agonist users and 136 (69.7%) were inhaled corticosteroid users.

Of the steroid users, 25 patients (18.4%) were identified as “new” users, *i.e.*, they have not been on inhaled steroids before the study. (This step was accomplished by examination of the patients’ prescription history from pharmacy prescription profiles). Of those, 17 patients (68%) showed a peak in utilization dollars during the month the steroid was added. This peak may have been related to the patients’ progressive decline in asthma control, resulting in higher utilization of drugs (including the addition of inhaled steroids), outpatient visits, emergency department visits, and hospitalizations.

Within the study sample, patients in the inhaled beta₂-agonist and the corticosteroid groups were similar with respect to age and gender.

Race/ethnicity was not available in the given database for analysis. The study sample had 9.8% more females than males. This proportion is comparable to the general U.S. asthmatic population, which reported a prevalence of 8.4% more females than males in 1995 (NHLBI 1999).

DISTRIBUTION OF EXPENDITURES

The results of this study showed that physician office visits accounted for the highest portion (41.1%) of total asthma-related expenditures, followed by hospitalizations (28.2%). These proportions are in contrast with the National Heart, Lung, and Blood Institute 1999 report (NIH 1999) which reported hospitalizations as the highest portion of the national asthma-related expenditures. This difference may be related to the characteristics of the study population. Military patients may be healthier than the general population, therefore, they are less likely to require inpatient care. The mean length of stay for the 13 inhaled steroid users with hospital admissions was 2.1 days, which is lower compared to the 1995 national average of 3.7 days (NIH 1999). On the other hand, the proportions of pharmacy (19.8%) and emergency department (10.8%) expenditures from the present study were almost identical to those of Lozano's estimates (19.9% and 10.5%, respectively).

TESTS OF HYPOTHESES

Objective 1

H₀1: There is no difference in the prescription use and drug acquisition costs between the inhaled corticosteroid and beta₂-agonist groups. Similar to previous work, prescription usage and associated costs were higher in the steroid group because the majority of these patients (96.3%) were receiving combination therapy versus the monotherapy in the beta₂-agonist group. Further, corticosteroids, especially the newer agents, cost considerably more than beta₂-agonists.

The mean number of prescriptions used in the steroid group was 3.1 more than the beta₂-agonist group. Similarly, drug acquisition costs were \$78.95 more in the steroid group than the beta₂-agonist group. Based on the results from the Mann-Whitney U tests, prescription use and acquisition costs were found to be statistically different between the two treatment groups; therefore, the null hypothesis was rejected.

Objective 2

H₀2: There is no difference in the utilization and costs for asthma-related physician visits between the inhaled corticosteroid and beta₂-agonist groups. The steroid group had a mean of 1.55 more physician visits than the beta₂-agonist group. The mean difference in associated cost was \$171.93 higher

in the steroid group. Results from the Mann-Whitney U tests showed that physician visits and associated costs for the two groups were statistically different, leading to the rejection of the null hypothesis. No distinction was made for scheduled versus unscheduled visits.

Objective 3

H₀3: There is no difference in the utilization and costs for asthma-related hospitalizations between the inhaled corticosteroid and beta₂-agonist groups. Patients in the beta₂-agonist group reported no hospital admissions, while 13 patients (9.6%) in the steroid group reported inpatient stays. The length of stay (LOS) was from 1 to 6 days, with a mean of 2.1 days. This is markedly lower than the 1987 national average LOS of 4.7 days (NIH 1999). The total inpatient cost of treating these 13 patients was \$27,318, translating to an average of \$2,101.38 per patient. In terms of inpatient days and associated costs, the Mann-Whitney U tests showed that the values were statistically different ($Z=-2.452$, $p=0.014$) between the two groups, and the null hypothesis was rejected. It was concluded that hospitalizations and associated costs between the two treatment groups are not equal.

Objective 4

H₀4: There is no difference in the utilization and costs for asthma-related emergency department (ED) visits between the inhaled corticosteroid and beta₂-agonist groups. The steroid group reported a mean of 0.20 more ED visits than the beta₂-agonist group. The mean cost for these episodes was \$33.13 higher for the steroid group than the beta₂-agonist group. Results from the Mann-Whitney U tests showed that ED visits and associated costs between the two groups were not significant ($Z=-1.590$, $p=0.112$), and the null hypothesis was not rejected.

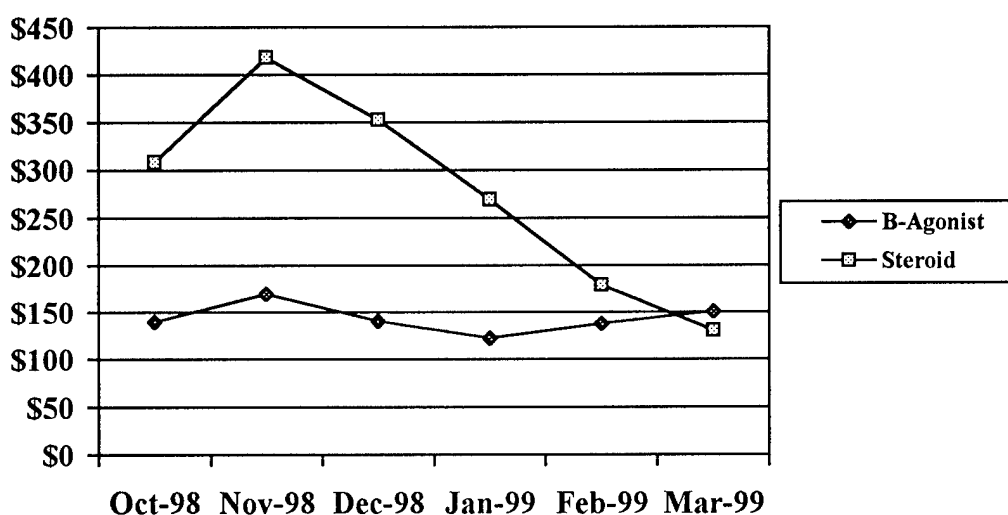
Objective 5

H₀5: There is no difference in the total cost of asthma-related health care utilization between the inhaled corticosteroid and beta₂-agonist groups. Overall, the steroid group reported a mean of \$484.88 more in total utilization cost than the beta₂-agonist group. Again, the biggest portion of this cost was in outpatient visits. Total health care costs between the two groups were found to be statistically different ($Z=-7.671$, $p<0.001$), and the null hypothesis was rejected. The conclusion was that the total utilization dollars between the two treatment groups are not equal.

These results were inconsistent with most published studies, which reported lower health care costs by steroid users. From the depiction of the

mean monthly health care costs shown in Figure 4.1, the costs for the beta₂-agonist users appeared to be considerably less than those of the steroid users, at least in the beginning of the study period. Both groups showed a peak in the month of November. This peak was partly contributed by a few “new steroid users” who incurred significant inpatient costs during this month. Following this peak, the steroid users showed a continuous decline in costs, and it even crossed the line for the beta₂-agonist group towards the end of the study period. The beta₂-agonist group, on the other hand, showed a decline in cost, and then began to rise in February and March. If stretched out further time-wise, the economic benefits of the steroid users may have been evident. However, without supporting data for a longer period of time, the potential economic benefits of steroid use for this study population remain a mere speculation.

Figure 4.1. Mean Asthma-Related Health Care Cost (1999 \$U.S.) by Treatment Group from October 1998 to March 1999.



SUBGROUP ANALYSIS (HIGH USERS)

Of the 195 patients in this study sample, 39 (20%) were identified as “high users.” For the purpose of this study, high users were defined as those with > 4 physician visits, > 1 emergency department visit, or > 12 prescriptions within the 6-month study period. This subgroup was predominantly inhaled steroid users—only three (7.7%) belonged to the beta₂-agonist group. Appendices K and L depict the age and gender distributions of this subgroup. The gender distribution of this subgroup was almost evenly split (48.7% females and 51.3% males). Age-wise, over half (53.8%) of this subgroup was made up

of children 19 years and under. About 33.3% were made up of patients between ages 20 and 49. The remaining 12.8% was made up of patients 50 and older. Within this subgroup, an estimate of 20.5% was made up of active-duty members between the ages of 20 and 49. Table 4.1 summarizes the characteristics of this subgroup.

Table 4.1. Characteristics of High Users by Age Category.

Variable	0 – 19 yrs	20 – 49 yrs	≥ 50 yrs	Total
Patients, No.	21 (53.8%)	13 (33.3%)	5 (12.8%)	39
Gender, No.				
Male	10 (47.6%)	7 (53.8%)	3 (60.0%)	20 (51.3%)
Female	11 (52.4%)	6 (46.2%)	2 (40.0%)	19 (48.7%)

Visual inspection of the Normal Q-Q plots for utilization and cost variables within this subgroup revealed that the distributions did not depart too much from normality. For the most part, the data points appeared to cluster around the Q-Q plot. Subsequently, an ANOVA (along with Tukey's HSD) was performed to test for differences in asthma-related utilization and costs for the above age groups (0-19 yrs., 20-49 yrs., and ≥ 50 yrs.). Table 4.2 summarizes the health care utilization for this subgroup.

Table 4.2. Asthma-Related Health Care Utilization for High Users by Age Category from October 1998 to March 1999.

Category	0 – 19 yrs Mean (S.D.) [Median] N = 21	20 – 49 yrs Mean (S.D.) [Median] N = 13	≥ 50 yrs Mean (S.D.) [Median] N = 5	ANOVA F Statistic (p)
Prescription, No.	10.33 (3.43) [11.00]	9.92 (5.62) [7.00]	12.00 (3.16) [13.00]	0.436 (0.650)
Physician office visits	4.10 (2.17) [4.00]	3.92 (2.36) [3.00]	2.40 (2.88) [1.00]	1.096 (0.345)
Inpatient days	0.38 (0.50) [0.00]	0.08 (0.28) [0.00]	0.0 (0.00) [0.00]	3.209 (0.052)
Emergency dept. visits	1.62 (1.53) [1.00]	0.54 (1.05) [0.00]	0.60 (0.89) [0.00]	3.117 (0.056)

The ≥ 50 age group had the highest level of prescription usage, followed by the 0–19 group, then the 20–49 group. Prescription use by “high users” are further depicted in Appendix M. Although not statistically significant (applying the Bonferroni’s correction, $\alpha=0.016$), young patients in the <20 age group used more medical services (physician visits, hospitalizations, and emergency department visits) than the other two age groups.

Representing a small portion of the study sample, the high-user group accounted for 44.6% of total health care expenditures. Although not statistically significant, children (<20 group) had the highest expenditures in inpatient and

emergency department visits, as well as the highest overall expenditures. Statistically significant differences in the physician visit costs and the drug acquisition costs were found. The 20-49 age group had statistically higher costs associated with physician visits ($p=0.010$) than the other two age groups. No differences were found between the 0-19 and the ≥ 50 age groups. It is interesting to note that the utilization of physician visits was highest in the 0-19 age group (mean 4.10), but not the highest in associated cost. Why the disparity between utilization and cost? The difference lies in the unit costs for Pediatrics versus Primary Care centers, which was \$63 versus \$151, respectively. Sixty-three dollars was used to compute the cost for physician office visits coded with Pediatric Services. Had the same cost unit been used in the calculation for the children group as the adult groups, the expenditure for all three medical components (physician visits, hospitalizations, and emergency department visits) would have been the highest in the < 20 age group.

The second statistical difference found was in drug acquisition costs between the ≥ 50 age group and the 0-19 age group ($p=0.015$). One reason for this difference is most likely due to the prescribing habits of physicians with regards to their pediatric asthmatic patients. The pediatric group received mostly beta₂-agonists and the “elderly” received mostly steroids, which are generally more costly than the beta₂-agonists. The ≥ 50 age group had a mean of \$277.05 versus the 0-19 age group of \$117.11 and the 20-49 age group of

\$149.65. Table 4.3 illustrates the asthma-related costs for the high-user subgroup.

Table 4.3. Asthma-Related Health Care Costs for High Users by Age Category from October 1998 to March 1999.

Cost Category	0 – 19 yrs Mean (S.D.) [Median] N = 21	20 – 49 yrs Mean (S.D.) [Median] N = 13	≥ 50 yrs Mean (S.D.) [Median] N = 5	ANOVA F Statistic (p)
Medical cost	\$1216 (1115) [578]	\$735 (438) [755]	\$460 (442) [326]	2.113 (0.136)
Inpatient	677 (1017) [0]	55 (197) [0]	0 (0) [0]	3.360 (0.046)
Outpatient	275 (156) [252]	592 (357) [453]	362 (435) [151]	5.298 (0.010)
Emergency	264 (250) [163]	88 (171) [0]	98 (146) [0]	3.117 (0.056)
Drug cost	117 (71) [105]	150 (123) [94]	277 (167) [295]	4.714 (0.015)
TOTAL	1333 (1118) [748]	884 (405) [820]	737 (442) [656]	1.556 (0.225)

ASSUMPTIONS AND LIMITATIONS

Several assumptions were made because of the limitations of using a prescription database and a retrospective study design. It was assumed that the patients were in compliance with the prescribed regimen and that they used the inhalers appropriately. It was also assumed that the ICD-9-CM codes for asthma diagnoses were entered correctly in the database. Even if accurate, ICD-9-CM codes for asthma do not provide adequate evidence regarding the severity of the disease. Thus, a four-months' prescription supply was used as a proxy for chronic disease status. Since prescription and health care services were free-of-charge to eligible beneficiaries, it was assumed that patients did not seek care outside the system. Many variables determine the frequency of physician office visits. These include the severity of the disease, compliance with the prescribed regimen, age of the patient, and concurrent illnesses that exacerbate the asthma. Distinction between scheduled and unscheduled office visits was not made in this study. Finally, it was assumed that the drug-related side effects were mild and did not incur additional cost.

Several limitations may have affected the results and validity of this study, and thus, the generalizability of it. This study was conducted using a retrospective database of a military institution, whose population characteristics may be markedly different from those of the general population. According to a December 6, 1999 report in *Army Times* (Maze 1999), the military medical

system provides care to approximately 8.2 million beneficiaries. Of those, 19% are active-duty members and 27% are their dependents, while retirees and their dependents make up approximately 53%.

Compared to previous work, the opposite results seen in this study are most likely influenced by the overall study design, which resulted in unbalanced and probably unequal groups. The results of this study may have been quite different had the study duration been longer (perhaps a year or two) and the sample size been larger. A different study design, such as pre/post or matched groups, certainly would have strengthened the results of this study. The limited accessibility of data (duration and disease status) precludes a stronger design.

Selection bias was a big factor in this study since patients were not randomized to treatment groups. Thus, patients in the inhaled steroid group may have been more progressive in their disease status to begin with than their counterparts in the inhaled beta₂-agonist group. This precondition certainly would have confounded the results of the study.

One final consideration to bear in mind is the cost differences. From drug acquisition to medical expenditures, these costs may apply to other military institutions but are quite different from non-military settings. Compared to the average wholesale price (AWP), the institution's acquisition costs of the study

medications were almost negligible (total acquisition cost was \$19,204 versus \$87,582 AWP).

IMPLICATIONS FOR DACH

Within the overall study sample, not any one particular age group appeared to stand out as potential candidates for special intervention. However, when subjects identified as “high users” were analyzed as a subgroup, it then appeared that asthmatics age 19 and under should be targeted for further intervention or education. It is no surprise that asthmatics in this age group--especially those under five or even as old as ten--generally have more difficulty with proper inhaler techniques than older patients, thus resulting in poorer disease management and greater health care utilization. It is a challenge, then, for policy makers, providers, and disease management coordinators to be creative in implementing programs that are as economical as they are effective in controlling asthma. Effective ways of teaching and reinforcing compliance with therapy (including proper inhaler techniques) could significantly decrease utilization and expenditures associated with this costly and burdensome disease.

Previous studies suggest that the long-term management of asthma should begin with inhaled steroid and that regular use of inhaled beta₂-agonist might lead to a worsening in asthma control. Based on the results of this study population, however, the same suggestions cannot be made without further

extensive investigation. There are still many issues affecting the pros and cons of using inhaled steroids as the first line treatment for asthma. In the TRUST study (Dennis *et al.* 2000) recently published in the May 13, 2000 issue of *The Lancet*, Dennis and colleagues found no evidence that the regular use of inhaled salbutamol increased the exacerbation rate of asthma in their study population. Rutten-van Molken and colleagues (1995) found clinical benefits from steroid use, but at a slight increase in health care costs.

SUGGESTIONS FOR FUTURE RESEARCH

Future studies using prescription and medical databases should be designed so as to incorporate a larger sample size and longer duration. Certainly, accurate data dealing with disease severity would lend greater support to the study.

Due to the recent introduction of the leukotriene modifiers, investigators have ample opportunity to compare the efficacy and economic implications between this drug class and the inhaled steroids. Finally, the effects of long-acting beta₂-agonists have yet to be fully explored.

CONCLUSION

It appeared from this report that, although the majority of the study sample was managed with inhaled steroids, not all providers were following the

national and international guidelines regarding the use of inhaled steroids for the management of persistent asthma. A number of providers are still reluctant to prescribe steroids because of the negative side effects associated with steroid use.

Although there are studies offering evidence regarding the economic benefits of inhaled steroid, the results from this study failed to offer parallel findings. Also in contrast to previous work, the regular beta₂-agonist users in the present study appeared to be well controlled in their asthma. Perhaps the reason for this is that these patients may have been milder in their disease severity than their counterparts in the steroid group. In summary, steroid users in this study population appeared to consume significantly more asthma-related health care services and incur higher associated costs. Again, these findings may be related to the notion that perhaps the steroid users in this population were sicker than the beta₂-agonist users, and thus, were more expensive to manage.

In light of the results from this study (and those of the TRUST study published this year), changes in the prescribing habits of providers at Darnall Army Community Hospital, to be more in line with national and international guidelines, do not appear to be warranted without further investigation. However, providers should stay informed of current guidelines and tailor appropriate asthma management for optimal patient outcomes.

Appendix A

Fields Included within the Composite Health Care System (CHCS) Prescription File

<u>FIELD</u>	<u>DEFINITION</u>
FMP/SSN	Family member prefix/social security #
AGE	Age at start of study
GENDER	Male or female
PATIENT	Name of patient
OP_REC_LOC	Location of medical records
DATE	Dispensing date
RX_NUM	Prescription number
DRUG	Name of drug dispensed
QTY	Quantity dispensed
AHFS	Drug classification number
ROUTE	Route of administration
DRUG_IEN	Internal control number for drug
PROVIDER	Name of prescriber
MEPRS	Clinic code
SIG	Directions for use
FILL#	Fill number
REFILL	Number of refills authorized

Appendix B

Fields Included within the Inpatient Data File

<u>FIELD</u>	<u>DEFINITION</u>
DISCH DATE	Discharge date
FMP/SSN	Family member prefix/social security #
MEPRS	Clinic code
CLINIC	Clinic name
DRG	Diagnosis Related Group code
DRG NAME	Diagnosis Related Group name
ICD9	ICD-9-CM code
DIAGNOSIS	Diagnosis
DAYS	Length of stay

Appendix C

Fields Included within the Ambulatory Data File

<u>FIELD</u>	<u>DEFINITION</u>
DATE	Date of visit
FMP/SSN	Family member prefix/social security #
MEPRS	Clinic code
CLINIC	Clinic name
ICD9	ICD-9-CM code
DIAGNOSIS	Diagnosis
VISIT	Visit number

Appendix D

Unit Costs Used in Computing Medical Care Expenditures

Department	Unit Cost
Outpatient	
Pediatric	\$63/visit
Primary Care	\$151/visit
Emergency	\$163/visit
Inpatient	\$711/day

Source: Costs shown are institutional averages obtained from DACH Resource Management Office; 1999 \$U.S.

Appendix E

Medications and Their Associated Costs Included in This Study

Generic Name	Trade Name	Class	Unit Cost per Canister
Albuterol	Proventil, Ventolin	Beta ₂ -agonist	\$ 1.61
Beclomethasone	Beclovent	Corticosteroid	\$17.20
Budesonide	Pulmicort	Corticosteroid	\$64.52
Flunisolide	Aerobid	Corticosteroid	\$17.91
Fluticasone	Flovent	Corticosteroid	\$10.80
Salmeterol	Serevent	Beta ₂ -agonist	\$17.97
Triamcinolone	Azmacort	Corticosteroid	\$ 9.32

Source: DACH pharmacy department; 1999 \$U.S.

APPENDIX F

ICD-9-CM Codes Used to Verify Diagnosis of Asthma

493.00	Extrinsic Asthma without Status Asthmaticus
493.01	Extrinsic Asthma with Status Asthmaticus
493.10	Intrinsic Asthma without Status Asthmaticus
493.11	Intrinsic Asthma with Status Asthmaticus
493.20	Chronic Obstructive Asthma without Status Asthmaticus
493.21	Chronic Obstructive Asthma with Status Asthmaticus
493.90	Asthma (unspecified) without Status Asthmaticus
493.91	Asthma (unspecified) with Status Asthmaticus

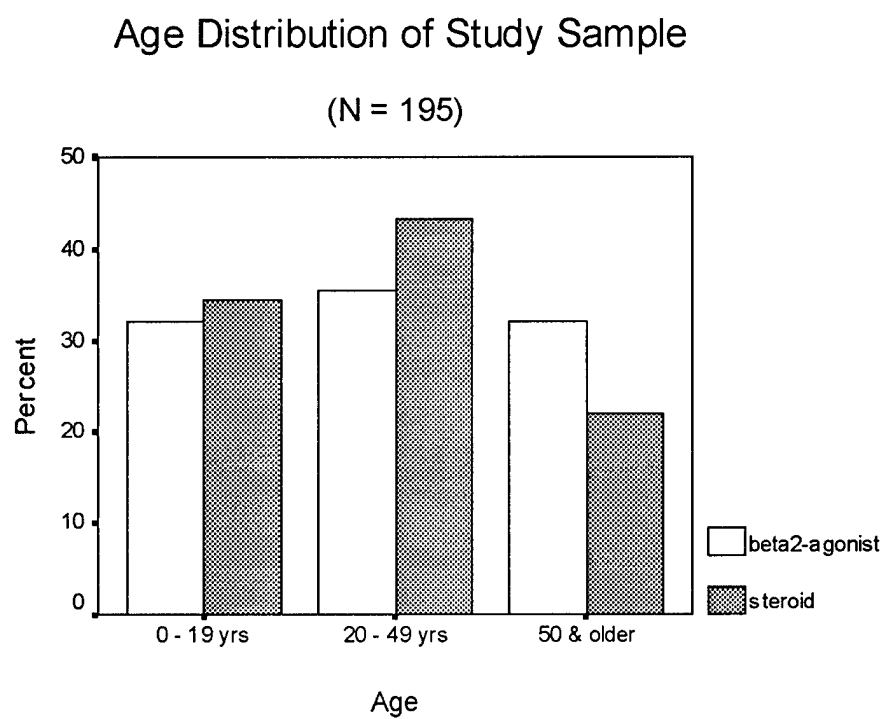
Appendix G

Tests of Normality

	Kolmogorov-Smirnov ^a		
	Statistic	df	Sig.
AGE	.107	195	.000
INPATIENT DAYS	.525	195	.000
OUTPAT VISITS	.206	195	.000
ER VISITS	.455	195	.000
# OF RX	.175	195	.000
INPAT COST	.520	195	.000
OUTPAT COST	.211	195	.000
ER COST	.455	195	.000
DRUG\$.140	195	.000

a. Lilliefors Significance Correction

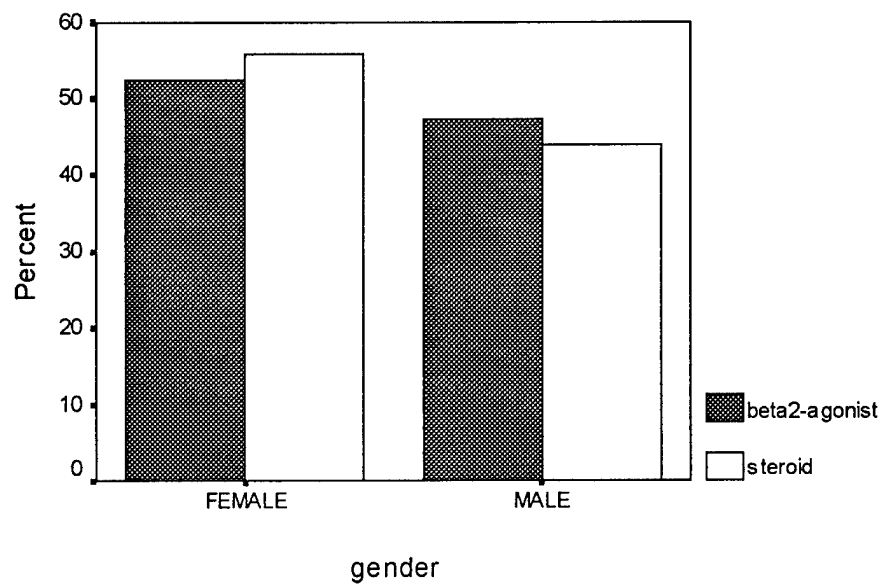
Appendix H



Appendix I

Gender Distribution of Study Sample

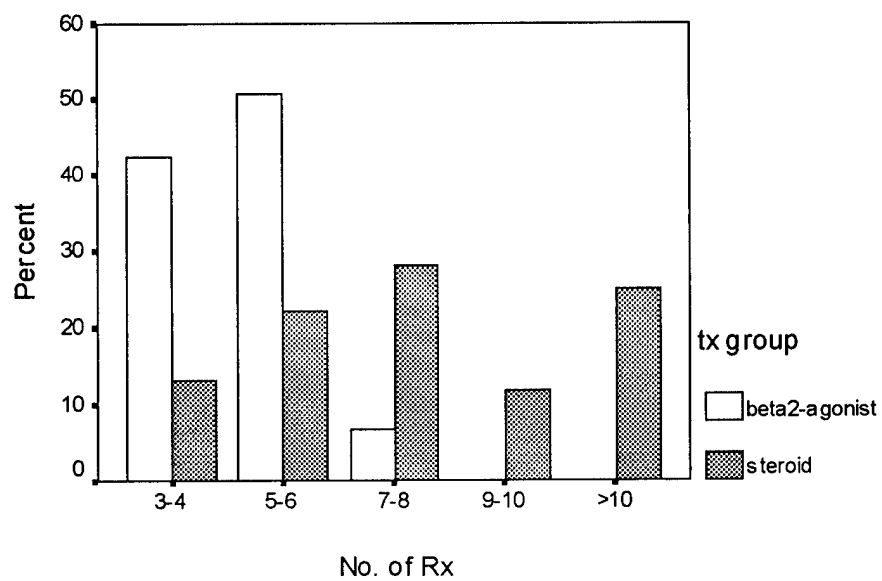
(N = 195)



Appendix J

Prescription Usage of Study Sample

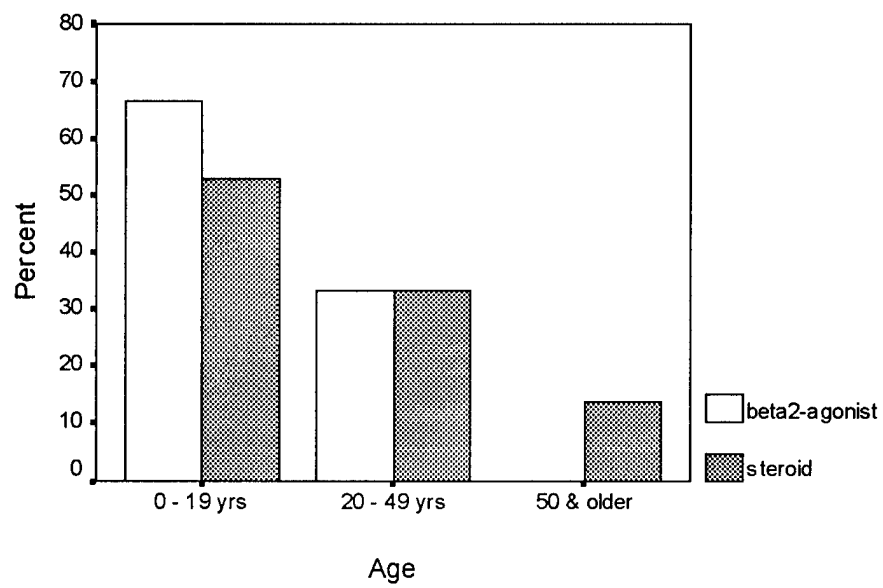
(N = 195)



Appendix K

Age Distribution of High Users

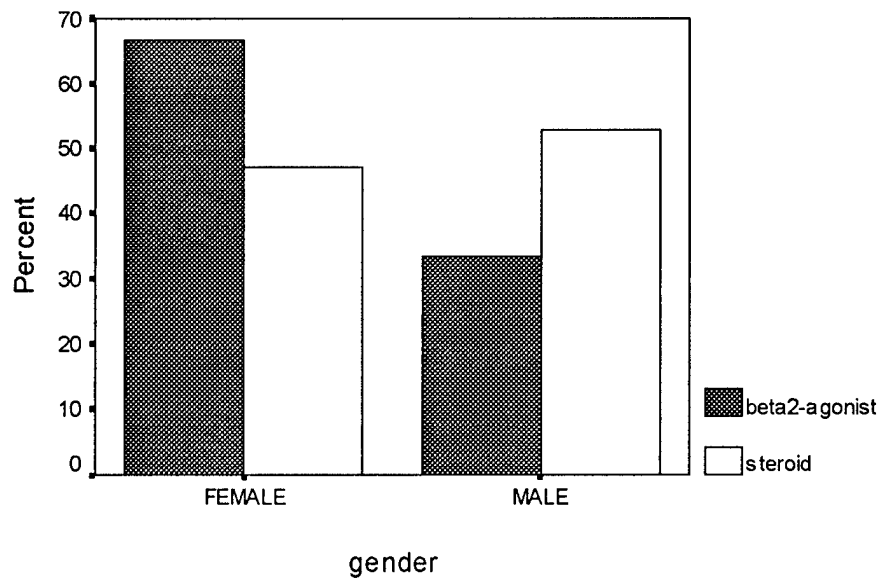
(N = 39)



Appendix L

Gender Distribution of High Users

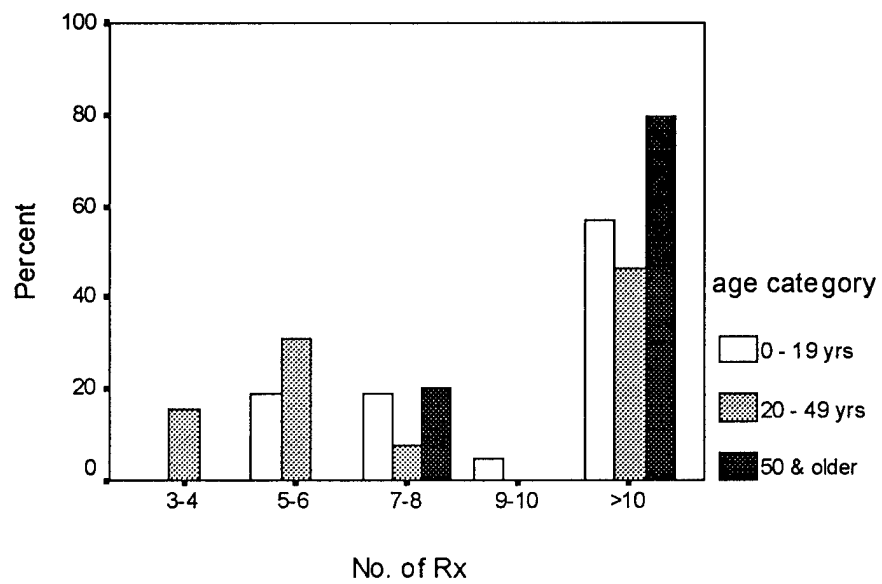
(N = 39)



Appendix M

Prescription Usage of High Users

(N = 39)



REFERENCES

- Adelroth E, Thompson S. Advantages of High-Dose Inhaled Budesonide. *Lancet*. 1988; 1(8583):467.
- Aldridge RE, Hancox RJ, Taylor DR, *et al*. Effects of Terbutaline and Budesonide on Sputum Cells and Bronchial Hyperresponsiveness in Asthma. *Am J Respir Crit Care Med*. 2000; 161:1459-64.
- Balkrishnan R, Norwood GJ, Anderson A. Outcomes and Cost Benefits Associated with the Introduction of Inhaled Corticosteroid Therapy in a Medicaid Population of Asthmatic Patients. *Clinical Therapeutics*. 1998; 20(3):567-80.
- Barbers R. Costs Associated with Asthma Treatment. *Current Opinion in Pulmonary Medicine*. 1998; 4:1-3.
- Barnes PJ, Pedersen S. Efficacy and Safety of Inhaled Corticosteroids in Asthma. *Am Rev Respir Dis*. 1993; 148:S1-S26.
- Barnes PJ. A New Approach to the Treatment of Asthma. *N Engl J Med*. 1989; 321(22):517-26.
- Barnes PJ. Current Therapies for Asthma: Promise and Limitations. *Chest*. 1997; 111:17S-26S.
- CDC. Asthma Mortality and Hospitalization Among Children and Young Adults—United States, 1980-1993. *MMWR*. 1996; 45(17):350-3.
- CDC. Asthma—United States, 1982-1992. *MMWR*. 1995; 43(51 & 52):952-5.
- Cumming R, Mitchel P, Leeder S. Use of Inhaled Corticosteroids and the Risk of Cataracts. *N Engl J Med*. 1997; 337:8-14.
- Dennis SM, Sharp SJ, Vickers MR, *et al*. Regular Inhaled Salbutamol and Asthma Control: The TRUST Randomised Trial. *Lancet*. 2000; 355: 1675-9.
- DeTullio PL, Corson ME. Effect of Pharmacist Counseling on Ambulatory Patients' Use of Aerosolized Bronchodilators. *Am J Hosp Pharm*. 1987; 44:1802-6.

DoD PEC. Management of Asthma. *Pharmacoeconomic Center Update*. Aug 1996; Vol. 96-11.

DoD PEC. *Pharmacoeconomic Center Update*. Mar 1999; Vol 99-5:8.

Donahue JG, Weiss ST, Livingston JM, *et al*. Inhaled Steroids and the Risk of Hospitalization for Asthma. *JAMA*. 1997; 277:887-91.

Doull I, Freezer N, Holgate S. Growth of Prepubertal Children with Mild Asthma Treated with Inhaled Beclomethasone Dipropionate. *Am J Respir Crit Care Med*. 1995; 151:1715-9.

Foresi A, Morelli MC, Catena E. Low-dose Budesonide with the Addition of an Increased Dose During Exacerbations is Effective in Long-term Asthma Control. *Chest*. 2000; 177:440-6.

Gergen PJ, Mullally DI, Evans R. National Survey of Prevalence of Asthma Among Children in the United States, 1976 to 1980. *Pediatrics*. 1988; 81:1-7.

Haahtela T, Jarvinen M, Kava T, *et al*. Comparison of a B₂-Agonist, Terbutaline, with an Inhaled Corticosteroid, Budesonide, in Newly Detected Asthma. *N Engl J Med*. 1991; 325:388-92.

Haahtela T, Jarvinen M, Kava T, *et al*. Effects of Reducing or Discontinuing Inhaled Budesonide in Patients with Mild Asthma. *N Engl J Med*. 1994; 331:700-5.

Hanania N, Chapman K, Sturtridge W, *et al*. Dose Related Decrease in Bone Density Among Asthmatic Patients Treated with Inhaled Corticosteroids. *J Allergy Clin Immunol*. 1995; 96:571-9.

Holt PR, Lowndes DW, Smithies E, Dixon GT. The Effect of Inhaled Steroids on the Hypothalamo-pituitary-adrenal Axis: Which Test Should Be Used? *Clin Exp Allergy*. 1990; 20:145-9.

Horowitz NJ, Kerns DG, Davies W. The Incidence of Known Diabetics among U.S. Army Active Duty Dental Patients. *Military Med*. 2000; 165 (5): 368-71.

International Classification of Diseases, Ninth Revision, Clinical Modification. Hyattsville, Md: US Department of Health and Human Services, Public Health Service. 1999.

Juniper EF, Kline PA, Vanzielegem MA, *et al.* Effect of Long-term Treatment with an Inhaled Corticosteroid (Budesonide) on Airway Hyperresponsiveness and Clinical Asthma in Nonsteroid-dependent Asthmatics. *Am Rev Respir Dis.* 1990; 142:832-6.

Katz Y, Lebas F, Medley H, *et al.* Fluticasone Propionate 50 mcg BID Versus 100 mcg BID in the Treatment of Children with Persistent Asthma. *Clinical Therapeutics.* 1998; 20(3): 424-37.

Larsen GL. Asthma in Children. *N Engl J Med.* 1992; 326: 1540-5.

Lenfant C. Role of the Pharmacist in Improving Asthma Care: National Asthma Education and Prevention Program. *Am J Health-Syst Pharm.* 1995; 52:1411-6.

Lozano P, Sullivan SD, Smith DH, *et al.* The Economic Burden of Asthma in US Children: Estimates from the National Medical Expenditure Survey. *J Allergy Clin Immunol.* 1999; 104: 957-63.

MacKinnon NJ, Flagstad MS, Peterson CR, Mesch-Beatty K. Disease Management Program for Asthma: Baseline Assessment of Resource Use. *Am J Health-Syst Pharm.* 1996; 53:535-41.

Mayo PH, Richman J, Harris W. Results of a Program to Reduce Admissions for Adult Asthma. *Ann of Int Med.* 1990; 112:864-71.

Maze R. GAO: Trim Redundant Military Health Care Services. *Army Times.* Dec 6, 1999.

McFadden ER, Gilbert IA. Asthma. *N Engl J Med.* 1992; 327:1928-36.

Mellis CM, Peat JK, Woolcock AJ. The Cost of Asthma: Can it be Reduced? *Pharmacoeconomics.* 1993; 3(3): 205-19.

Metso T, Kilpio K, Bjorksten F, *et al.* Detection and Treatment of Early Asthma. *Allergy.* 2000; 55: 505-9.

NIH. *Data Fact Sheet: Asthma Statistics.* National Heart, Lung, and Blood Institute. Jan 1999.

NIH. *Expert Panel Report II: Guidelines for the Diagnosis and Management of Asthma*. National Heart, Lung, and Blood Institute. 1997. HLBI Pub 97-4051.

Norusis MJ. *SPSS 8.0 Guide to Data Analysis*. Chicago, IL, Prentice-Hall, Inc. 1998; 91-107.

Pal S. Asthma Mortality Continues to Rise. *US Pharmacist*. 1997; 1(1):12.

Perera BJC. Efficacy and Cost Effectiveness of Inhaled Steroids in Asthma in a Developing Country. *Archives of Disease in Childhood*. 1995; 72:312-6.

Portyansky E. Newly Released Medical Guide Helps Treat Childhood Asthma. *Drug Topics*. 1999 (Nov 15):26, 33.

Ross RN, Morris M, Sakowitz SR, *et al*. Cost-Effectiveness of Including Cromolyn Sodium in the Treatment Program for Asthma: A Retrospective, Record-Based Study. *Clinical Therapeutics*. 1988; 10 (2):188-203.

Rutten-van Molken MPMH, Van Doorslaer EKA, Jansen MCC, *et al*. Costs and Effects of Inhaled Corticosteroids and Bronchodilators in Asthma and Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med*. 1995; 151:975-82.

Sears MR. Short-acting Inhaled β -agonists: To Be Taken Regularly or As Needed? *Lancet*. 2000; 355 (5): 1658-9.

Self TH, Nahata MC. Improving Outcomes in Asthma: Role of Pharmacy. *Annals of Pharmacotherapy*. 1997; 31:495-7.

Slack MK, Brooks AJ. Medication Management Issues for Adolescents with Asthma. *Am J Health-Syst Pharm*. 1995; 52:1417-21.

Sleath B, Collins T, Kelly HW, *et al*. Effect of Including Both Physicians and Pharmacists in an Asthma Drug-Use Review Intervention. *Am J Health-Syst Pharm*. 1997; 54:2197-200.

Smith DH, Malone DC, Lawson KA, *et al*. A National Estimate of the Economic Costs of Asthma. *Am J Respir Crit Care Med*. 1997; 156:787-93.

SPSS 9.0 for Windows, SPSS Inc. Chicago, IL; 1998.

Stempel DA, Durcannin-Robbins JF, Hedblom ED, *et al*. Drug Utilization Evaluation Identifies Costs Associated with High Use of Beta-adrenergic Agonists. *Ann Allergy Asthma Immunol*. 1996; 76:154-8.

Taylor WR, Newacheck PW. Impact of Childhood Asthma on Health. *Pediatrics*. 1992; 90: 657-62.

Verberne A, Frost C, Roorda R, *et al*, and the Dutch Paediatric Asthma Study Group. One Year Treatment with Salmeterol Compared with Beclomethasone in Children with Asthma. *Am J Respir Crit Care Med*. 1997; 156:688-95.

Weiss KB, Gergen PJ, Hodgson TA. An Economic Evaluation of Asthma in the United States. *N Engl J Med*. 1992; 326: 862-6.

Weiss KB, Sullivan SD. The Economic Costs of Asthma: A Review and Conceptual Model. *Pharmacoeconomics*. 1993; 4(1):14-30.

Weitzman M, Gortmaker SL, Sobol AM, Perrin JM. Recent Trends in the Prevalence and Severity of Childhood Asthma. *JAMA*. 1992; 268:2673-7.

Wong CA, Walsh LJ, Smith CJ, *et al*. Inhaled Corticosteroid Use and Bone-mineral Density in Patients with Asthma. *Lancet*. 2000; 355:1399-403.

VITA

Trish Bui was born in Vung Tau, Vietnam on August 17, 1964. She graduated from St. Frederick High School in Monroe, Louisiana in May 1983. She earned a degree of Bachelor of Science in Pharmacy from Northeast Louisiana University in December 1990. In September 1991, she received a commission from the U.S. Air Force as second lieutenant, and was assigned to Little Rock AFB in various positions from staff pharmacist to Chief of Pharmacy Services until June 1996. She then accepted the post of Commander of Diagnostics and Therapeutics Flight at Andersen Air Force Base for two years. With a military scholarship, Trish began her graduate studies at The University of Texas at Austin in August 1998 to obtain a degree of Master of Science in Pharmacy.

Permanent Address: 826 Delouche Street
Monroe, Louisiana 71202

This thesis was typed by the author.